REMARKS

Claims 1, 4-5, 9-18 and 20-29 are pending in the present application. Claims 2-3, 6-8, and 19 are cancelled. Claims 1, 4-5, 9-18, and 20-29 are amended. Support for the amended claims is described herein below.

Applicants have amended claim 1 to specify that foetel origin and prenatal diagnosis are determined from a single cell; i.e. a pre-amplified genome of a single trophoblastic and/or syncytiotrophoblastic cell. Foetal origin is specifically assessed by marker amplification of the trophoblastic and/or syncytiotrophoblastic pre-amplified genome.

Specifically, step a) of amended claim 1 recites "filtering a sample of pure or diluted maternal blood on a filter which has a pore size of between 6 and 15 μm, whereby epithelial cells are retained onto said filter[.]" Support for a " pore size of between 6 and 15 μm" is found in claim 23 in the specification as filed. Support for "whereby epithelial cells are retained onto said filter" is on page 8 at lines 7-8 in the specification as filed.

Step b) of amended claim 1 recites "analyzing the cells retained on the filter for the presence of at least one immunological or cytological marker, which is characteristic of trophoblastic and/or syncytiotrophoblastic cells, to identify trophoblastic and/or syncytiotrophoblastic cells; and individually collecting at least one cell, which has been identified as being a trophoblastic and/or syncytiotrophoblastic cell, whereby a single cell, which is presumed to be of foetal origin, or a collection of single cells, which are presumed to be of foetal origin, is obtained[.]" Support for the phrase "at least one immunoglogical or cytological marker, which is characteristic of trophoblastic and/or syncytiotrophoblastic cells", is found on page 10, at lines 5-6, 10-12 and 22-24 in the specification as filed. Support for "individually collecting" is found in claim 3 as filed in the original specification.

Step c) recites "lysing the single cell of step b), or a single cell of the collection obtained at step b), whereby the genome of this single cell is made accessible to amplification primers," and

step d) recites "amplifying the genome of the lysed single cell obtained at step c), whereby a pre-amplification product is obtained from a single cell[.]" Support for the lysis of a single cell and pre-amplification of its genome is found on page 14 at line 10 in the specification as filed.

Step e) recites "using the pre-amplification product obtained at step d), both to demonstrate the foetal origin of the single cell, and to carry out the prenatal diagnosis, wherein: i. said pre-amplification product is analyzed for the presence of genetic or polymorphism marker(s), which can, or the allelotyping of which can, be distinguished from the one(s) of a maternal cell genome, by amplification of said marker(s) from said pre-amplification product, whereby said presence demonstrates the foetal origin of said single cell, and ii. if said foetal origin is demonstrated, identifying at least one genetic or chromosomal anomaly of the foetus, or a genotype thereof, by genetic analysis of said pre-amplification product." Support for step e) is found on page 12 at lines 15-21, on page 14 at lines 16-18 (demonstration of the foetal origin by amplification of marker(s) from the pre-amplified product), on page 14 at lines 13-15 and on page 7 at lines 9-10 (prenatal diagnosis carried out on the pre-amplified product) in the specification as filed.

Additionally, claim 9 has been amended to recite that the "identification of a genetic or chromosomal anomaly of the foetus is carried out by identifying a genetic target." Support for claim 9 is found, *inter alia*, on page 12, at lines 1-3. Claim 24 has been amended to recite "pore/cm^2" as suggested by the Examiner. Support for this amendment is found on page 9 of the specification. Claim 25 has been amended to recite "all of the pores of said polycarbonate filtration membrane have a substantially identical diameter." Support for this amendment can be found in the application as filed, *inter alia*, on page 9 at line 12.

Claims 2, 3, and 6-8 have been cancelled due to redundancy in view of amended claim 1. Claims 1-29 have been amended to remove awkward language, e.g. "characterized in that" has been replaced with "wherein." Claims 18, 26, 28 and 29 have been amended to correct antecedent basis. Claims 23, 27 and 28 have been amended to remove the term "preferably" as suggested by the Examiner. Claims 26-29 have been amended to recite process steps as suggested by the Examiner. The phrase "ISET filtration device has been omitted from claims 27-29, to more accurately define the invention. Claims 9-18 and claims 20-25 have been amended to remove improper multiple dependencies.

Applicants submit that the amendments to the claims are supported throughout the specification and do not raise any issue of new matter.

Specification

The Examiner has objected to the specification because it includes the phrase "Key to the Figures." Applicants have amended the specification on page 19 at line 21 to recite "BRIEF DESCRIPTION OF THE DRAWINGS", instead of "KEY TO THE FIGURES", as suggested by the Examiner. Accordingly, Applicants request that this objection be withdrawn.

The Examiner has also objected to the specification because the application does not include a paper copy and computer-readable form (CRF) of the sequences contained in the specification. As requested by the Examiner, the Applicants have submitted herewith a new CRF and paper copy of the Sequence Listing. Additionally, Applicants have directed entry of the Sequence Listing into the specification and have provided herewith a declaration stating that the content of the paper and computer readable copies are the same. Furthermore, the Applicants have amended the specification on page 22 to include SEQ ID NOs. next to the sequences contained in the specification corresponding to those in the sequence listing. Accordingly, Applicants respectfully request that this objection be withdrawn.

Claim Objections

The Office Action states that claims 9-18 and 20-25 are objected to because these are multiple dependent claims that depend on other multiple dependent claims. Claims 9-18 and 20-25 have been amended to remove the inappropriate dependencies. Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

Claim 24 also is objected to because it recites "pores/m^2." Claim 24 has been amended to recite pore/cm^2 according to the Examiner's suggestion. Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

Claim rejections – 35 USC §101

Claims 26-29 are rejected under 35 U.S.C. §101 for not reciting process steps. Applicants respectfully traverse.

Claims 26-29 have been amended into process claims and recite process steps. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim rejections – 35 USC §112, second paragraph

Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action states that claims 1-25 are indefinite because the phrases "in particular" "particularly", and "certain circulating cells", are unclear. The phrases "in particular" and "certain circulating cells" have been removed from claim 1, which now recites, "filtering a sample of pure or diluted maternal blood on a filter, which has a pore size of between 6 and 15 μm, whereby epithelial cells are retained onto said filter." The phrase "in particular" has been removed from 17, which recites "wherein the foetal origin is demonstrated by identifying a marker or a combination of markers, the presence of which, or the allelotyping of which, is

specific to the DNA of paternal cells." The term "particularly" was not present in the original claim set. Accordingly, no amendments were made regarding this term. Additionally, claims 4-5, 9-16-18, 20-25 do not recite the allegedly unclear phrases described above and are dependent on claims that do not recite these phrases. Claims 2-3, 6-8 and 19 are cancelled. Accordingly, Applicants respectfully request that the 112, second paragraph, rejection be reconsidered and withdrawn.

The Office Actions states that claims 1-25 are indefinite over the recitation of "certain enriched cells", because the claims previously refer to a step of concentrating cells, rather than enriching cells. Moreover, the Office Action states that the claims do not clearly set forth how to select the "certain" cells. Claim 1 has been amended to remove this phrase. Claims 4-5, 9-16-18, 20-25 do not recite this allegedly unclear phrase and are dependent on claims that do not recite the phrase. Claims 2-3, 6-8 and 19 are cancelled. Accordingly, Applicants respectfully request that the 112, second paragraph, rejection be reconsidered and withdrawn.

The Office Action states that claims 1-25 are indefinite over the recitation of "identifying genetic anomalies specifically targeted to individually analyze cellular genomes for which a foetal origin has been demonstrated" because this phrase is unclear. Claim 1 has been amended to recite "identifying at least one genetic or chromosomal anomaly of the foetus." Because the meaning of identifying an anomaly of a foetus", is clear to a skilled artisan, claim 1 is not indefinite. Claims 4-5, 9-16-18, 20-25 do not recite the allegedly unclear phrase and are dependent on claims that do not recite this phrase. Claims 2-3, 6-8 and 19 are cancelled. Accordingly, Applicants respectfully request that the 112, second paragraph, rejection be reconsidered and withdrawn.

The Office Action states that claims 2-18 and 20-25 are indefinite over the recitation of "seeking genetic markers characteristic of foetal cells" because the phrase is unclear. The Office Action states that it is unclear as to whether the claims include a general method step of identifying new foetal cell markers or if the claims are intended to include an additional step in which the cells are analyzed for foetal cell specific markers.

Amended claim 1 does not recite the allegedly indefinite above-referenced phrase. Claim 1 recites "said pre-amplification product is analyzed for the presence of genetic or polymorphism marker(s), which can, or the allelotyping of which can, be distinguished from the one(s) of a maternal cell genome, by amplification of said marker(s) from said pre-amplification product, whereby said presence demonstrates the foetal origin of said single cell. Additionally, this phrase has been removed from claim 17, which now recites "by identifying a marker or a combination of markers, the presence of which, or the allelotyping of which, is specific to the DNA of paternal cells. Claims 4-16 and 20-25 do not contain the allegedly indefinite phrase and depend from claims that have been amended to remove the unclear language. Claims 2-3, 6-8 and 19 have been cancelled. Accordingly, Applicants respectfully request that this rejection of claims 2-18 and 20-25 be reconsidered and withdrawn.

The Office Action states that claims 4-18 and 20-25 are indefinite over the recitation of the "the filtration membrane" because this phrase lacks proper antecedent basis since claim 4 recites the term "filter." These claims have been amended to correct the antecedent errors. Accordingly, Applicants respectfully request that the rejection of claims 4-18 and 20-25 be reconsidered and withdrawn.

The Office Action states that claims 8-18 and 20-25 are indefinite over the recitation of "genetic markers or of polymorphism, of a combination of said markers." The Office Action states that it is not clear as to how the recitation of the combination of markers further limits the claims or relates to the remainder of the claims. The Office Action, additionally, states that these claims are indefinite due to the recitation of the phrase "or of a particular allele assay of said

markers" because it is not clear as to whether the claims are intended to include a step of performing an allele assay or whether the claims include a step of identifying a marker that was found/identified in a "particular allele assay of said markers." Furthermore, the Office Action states that claims 17 and claims 20-25 are indefinite over the recitation of "on allele assay of said markers distinguished from those detected on the genome of non maternal cells."

Claim 11 has been amended to recite "said genetic or chromosomal anomaly of the foetus, or particular genotype thereof, is identified by amplification of one or more sequence(s) carrying the genetic target(s), from said pre-amplification product". Claim 17 has been amended to recite "by identifying a marker or a combination of markers, the presence of which, or the allelotyping of which, is specific to the DNA of paternal cells". Claim 8 has been cancelled. Claims 9-18 and 20-25 have been amended and do not depend on claim 8. Claims 9-18 and 20-25 do not recite these phrases. Because a skilled artisan understands the amended phrases as recited above, claims 8-18 and 20-25 are not indefinite. Applicants respectfully request the rejection be reconsidered and withdrawn.

The Office Action states that claims 9-18 and 20-25 are indefinite because it is not clear as to what is intended to be meant by a genetic or chromosomal anomaly being "carried out by identifying a genetic target." Claim 9 has been amended to recite that "the identification of a genetic or chromosomal anomaly of the foetus is carried out by identifying a genetic target." Claims 10-18 and 20-25 do not contain the allegedly unclear phrase and do not depend on a claim reciting this phrase. Because a skilled artisan would understand the phrase "the identification of a genetic or chromosomal anomaly of the foetus is carried out by identifying a genetic target" claims 9-18 and 20-25 are not indefinite. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Office Action states that claims 18 and 20-25 are indefinite over the recitation of "and of a pre-amplified DNA preparation of cells or maternal origin or non foetal reference cells" because it is not clear as to how this recitation further limits the claims. Claim 18 has been

amended to recite "of a preamplifed DNA preparation of cells of maternal origin or of non foetal reference cells." Because a skilled artisan understands the scope of amended claim 18, this claim is not indefinite. Amended claims 20-25 do not recite the allegedly unclear phrase. Accordingly, Applicants request that this rejection be reconsidered and withdrawn.

The Office Action states that claims 19-25 are indefinite because it is not clear as to how the recitation set forth in these claims relates to the remainder of the claims because the claim do not refer to a method of determining the sex of a foetus. Additionally, the Office Action states that the phrase "chromosomal anomaly of the gender to be detected on the genome of cells", is unclear. Amended claims 20-25 do not recite the allegedly unclear phrase and claim 19 has been cancelled. Accordingly, Applicants respectfully request the rejection to claims 19-25 be reconsidered and withdrawn.

The Office Action states that claim 25 is indefinite for reciting the phrase "pore size of which is graded", because the specification does not provide a complete definition for this phrase and there is no art recognized definition for what is intended to be encompassed by graded pore sizes and one can not, therefore, determine the metes and bounds of the claimed subject matter. Claim 25 has been amended to recite "the filter is a polycarbonate filtration membrane, and in that all of the pores of said polycarbonate filtration membrane have a substantially identical diameter." Because a skilled artisan would understand the scope of amended claim 25, this claim is not indefinite. Accordingly, Applicants respectfully request this rejection be withdrawn.

The Office Action states that claims 26-29 are indefinite because they recite the term "preferably." Claims 26-29 have been amended to remove this term. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 26-29 are allegedly indefinite because the claims provide for the use of a filtration device, but do not set forth any steps involved in the process. Claim 26 has been amended to explicitly recite a step. Claim 27-29 depend on claim 26 and therefore, incorporate a step.

Accordingly, Applicants respectfully request that the rejection of claims 26-29 be reconsidered and withdrawn.

Claims 26-29 are allegedly indefinite over the recitation of "certain circulating cells." The Office Action states that it is "unclear as to which circulating cells are being referred to." Claim 26 has been amended to delete this phrase and to recite "a porous filter, which has a pore size of between 6 and 15 μm." Claims 27-29 do not recite the allegedly unclear phrase and depend on amended claim 26. Because a skilled artisan would not find the amended phrase to be unclear, claims 26-29 are not indefinite. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 26-29 are indefinite over the recitation of " the upstream block and "downstream block" because the phrases lack proper antecedent bases. Claim 26 has been amended to remove these phrases and now recites "upstream clamping device" and "downstream clamping device" to clearly refer to the clamping devices, which are "upstream and downstream with respect to the filtration direction." Accordingly, claim 26 is not indefinite. Claims 27-29 do not recite the allegedly unclear phrase and depend from claim 26. Accordingly, Applicants respectfully request this rejection to claims 26-29 be reconsidered and withdrawn.

Claims 27-29 are allegedly indefinite over the recitation of "a ISET type filtration device" because it is unclear, and "the applied filtration pressure" because it lacks proper antecedent basis. Claim 27-29 have been amended to remove the phrase "a ISET type filtration device" and to remove the antecedent errors. Accordingly, Applicants respectfully request this rejection to claims 26-29 be reconsidered and withdrawn.

Claims 28-29 are allegedly indefinite because it is unclear as to whether the filter referred to therein is the same as or distinct from the porous filter recited in claims 26 and 17. Claims 28-29 have been amended to recite "said filter." Claims 28-29 are not dependent on claim 17. Because a skilled artisan would understand that amended claims 28-29 refer to the porous filter

of claim 26, the claims are not indefinite. Applicants respectfully request this rejection to claims 28-29 be withdrawn.

The Office Action states that claim 29 is indefinite over the recitation of "pore density in the range of 5 X 10^4 to 5 X 10^5" because the claim does not set forth the units for the pore density and thereby is unclear as to whether the density is with respect to 1 mm or 1 cm or 1 m, etc. Claim 29 has been amended to recite "in the range of 5 x 10^4 to 5 x 10^5 pores/cm^2. Because amended claim 29 is clear to a skilled artisan, this claim is not indefinite. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. 102

Vona et al., 2002

Claims 1-14, 16-17, 19-23 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Vona *et al.*, 2002. Applicants respectfully traverse.

Attached to this response, is a verified translation of the priority document FR 01/05824, filed April 30, 2001. The Vona *et al.* reference has a later filing date of January, 2002. Thus, the Vona *et al.* reference is not available as prior art. Withdrawal of the rejection is warranted and respectfully requested.

WO 99/15892 to Kalionis

Claims 1, 2, 19-21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/15892 to Kalionis ("Kalionis"). Applicants respectfully traverse.

The Kalionis reference discloses a method for prenatal diagnosis, wherein the maternal blood is filtered on a 10 μm pore filter. (See claim 3, and page 4, at line 14, of the Kalionis reference). The cells retained on the filter are washed from the filter and re-suspended in a buffer. (See §(4), bridging pages 7 and 8). The aliquots of the cell suspension are pipetted onto a solid support, such as a glass microscope slide. (See end of §(4) on page 8, at lines 1-2). The

cells on the solid support are subjected to immunostaining with trophoblast-reactive antibodies, or *in situ* hybridization using a probe specific to trophoblast mRNA in order to identify and quantify the trophoblasts among the cells that have been deposited on the solid support. (See claims 5 and 9 of the Kalionis reference). Prenatal diagnosis is determined by analysis of the chromosomal content of trophoblastic cells using *in situ* hybridization of probes, which are specific for chromosomes in the nucleus of trophoblast cells (See claim 24 of the Kalionis reference).

In contrast, amended claim 1 is drawn to the demonstration of foetal origin and prenatal diagnosis on a single cell, more precisely on the pre-amplified genome of a single (trophoblastic) cell. The demonstration of foetal origin is presumed by the amplification of markers from the pre-amplified genome of the single cell. The single cell is lysed before the demonstration of foetal origin and the prenatal diagnosis is carried out on the same pre-amplified genome after the foetal origin has been demonstrated.

We respectfully submit that the Kalionis reference does not disclose the demonstration of foetal origin and prenatal diagnosis on a single cell. Instead, this reference discloses separating a cell fraction from maternal blood, wherein this fraction comprises various cell types. Hence, contrary to the claimed invention, the Kalionis reference does not disclose that the demonstration of the foetal origin is achieved on an individually isolated or collected cell, the foetal origin of which is presumed. Furthermore, this reference does not disclose that the prenatal diagnosis is carried out on an individually isolated or collected cell, the foetal origin of which is demonstrated.

Additionally, the Kalionis reference, which teaches the use of *in situ* hybridization for genetic analysis, does not disclose the cell lysis of the instant invention. On the contrary, the Kalionis reference teaches keeping the cells as intact as possible. (See, e.g., page 10 at line 3, page 13 at lines 15-16 "preserve cell morphology").

Moreover, the Kalionis reference does not disclose the use of nucleic acid amplification. More particularly, the Kalionis reference does not disclose the pre-amplification of the genome of a single cell or the demonstration of foetal origin and prenatal diagnosis from the pre-amplified genome.

Furthermore, we respectfully submit that the Kalionis reference does not disclose that the foetal origin is established by 1) the determination of a presumption of foetal origin (by immunostaining or cytology), and 2) the demonstration of its foetal origin by amplification of appropriate markers, if the cell is presumed of being of foetal origin.

Because the Kalionis reference does not disclose each and every element of claim 1, the Kalionis reference does not anticipate this claim. Claims 20-21 and 23 are dependent on claim 1 and are allowable at least by virtue of dependency. Claims 2 and 19 are cancelled. Therefore, Applicants respectfully request that the rejection to claims 1, 2, 19-21 and 23 be reconsidered and withdrawn.

US Patent No. 5,306,420 to Bisconte

Claims 26 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,306,420 to Bisconte ("Bisconte"). Applicants respectfully traverse.

The Bisconte reference discloses a method for filtering cells, wherein the method requires the use of a filtration device comprising: a porous filter that can retain cells based on size, wherein the filter is mounted between an upstream and a downstream clamping device; a filtration seal; a means for storing or pre-treating samples, which is upstream of the filter; a perforated gasket facing a storage means which is downstream of the filter; and a means for forced filtration (i.e. a pressure device or a suction device).

In contrast, amended claims 26 and 27 recite active process steps; namely, amended claim 26 recites that the claimed process comprises filtering maternal blood, and amended claim

27 recites that the claimed process comprises applying pressure on the filter, wherein said applied pressure is in the range of 0.05 to 0.8 bar.

The Bisconte reference does not disclose each and every element of claims 26-27. Specifically, Bisconte does not disclose the filtering of maternal blood or the application of a pressure of 0.05-0.8 bar.

Therefore, for the above reasons, the Bisconte reference does not anticipate claims 26-27. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim rejections – 35 U.S.C. §103

Vona (2002) in view of US Patent No. 6,309,822 to Fodor

Claim 15 is rejected under 35 USC §103 as being unpatentable over Vona *et al.* (2002) in view of US Patent No. 6,309,822 to Fodor ("Fodor"). Applicants respectfully traverse.

As stated above, the Vona *et al.* (2002) reference is not available as prior art because submitted herewith is a translation of a French priority document with a filing date of April 30, 2001, which pre-dates the Vona *et al.* 2002 reference. Therefore, the Fodor reference can not be combined with Vona *et al.*, and no *prima facie* case of obviousness is presented. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Vona et al. (2002) in view of US Patent No. 6,159,685 to Pinkel

Claim 18 is rejected under 35 USC §103 as being unpatentable over Vona et al. (2002) in view of US Patent No. 6,159,685 to Pinkel ("Pinkel"). Applicants respectfully traverse.

As explained above, the Vona *et al.* (2002) reference is not available as prior art. Therefore, the Pinkel reference cannot be combined with Vona *et al.* (2002). The Pinkel reference relates to Comparative Genomic Hydridization (CGH), and does not disclose teach or suggest the all of the elements incorporated into claim 18. Because no *prima facie* case of

obviousness is presented, claim 18 is not obvious in view of Pinkel. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Vona et al. (2002)

Claim 24 is rejected under 35 USC §103 as being unpatentable over Vona *et al.* (2002). Applicants respectfully traverse.

As explained *supra*, the Vona *et al.* 2002 reference is not available as prior art reference. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Kalionis in view of Vona et al., 2000

Claims 1-7, 9-12, 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/15892 to Kalionis ("Kalionis") in view of Vona *et al.* 2000. Applicants respectfully traverse.

As described *supra*, the Kalionis reference does not disclose, teach or suggest the isolation and lysis of an individual cell, the use of nucleic acid amplification and the pre-amplification of the genome of a single cell for the prenatal diagnosis of foetal cells. More particularly, the Kalionis reference does not disclose, teach or suggest the demonstration of both foetal origin and prenatal diagnosis from a single pre-amplified genome. Even more particularly, the Kalionis reference fails to disclose teach or suggest that foetal origin can be established by: 1) the determination of a presumption of foetal origin (by immunostaining or cytology), and 2) if the cell is effectively presumed of being of foetal origin, the demonstration of its foetal origin by the amplification of appropriate markers.

Likewise, the Vona *et al.*, 2000 reference does not disclose these elements. The Vona *et al.* 2000 reference discloses the Isolation by Size of Epithelial Tumor cells (ISET). More particularly, the Vona *et al.* 2000 reference teaches the isolation of individual epithelial tumor cells by filtration of the Hep3B cell line according to cell size, the microdissection of the filter to

collect a single tumor cell, the DNA extraction from the single collected cell, and the PCR amplification of the extracted DNA with p53 primers. However, the Vona *et al.* 2000 reference fails to teach how the p53 detection process is used for prenatal diagnosis.

The Vona *et al.,* 2000 reference does indicate, however, that the ISET process may have potential uses in the isolation of trophoblastic cells from the peripheral blood of pregnant women. But, these indications are only a hypothetical suggestion. For example, Vona *et al.* 2000 states that "the isolation of trophoblastic cells from the peripheral blood of pregnant women has been *initiated*", emphasis added) and the ISET process "*may constitute an important step* towards improving the prenatal diagnosis of genetic diseases" (See page 62, right-hand column, last paragraph, emphasis added). Moreover, the reference states "further studies (...) have to be performed to define the size threshold of ISET application" (see page 62, left-hand column, last line of first paragraph). Hence, this reference does not contain any disclosure or enabling guidance as to how such a prenatal diagnosis could be conducted.

Additionally, we submit that the Vona *et al.*, 2000 reference, which suggests combining "immunomorphological studies with novel assays exploring genetic abnormalities in individual isolated cells" in the context of oncology (see page 62, right-hand column, beginning of first paragraph), does not suggest combining immunomorphological studies and the analysis of genetic abnormalities with assays for demonstrating the foetal origin, and, more particularly, with assays for demonstrating the foetal origin of a single cell by amplification of genetic markers.

Finally, the Vona *et al.* 2000 reference does not disclose, teach, or suggest the elements of the instant claims. Particularly, the Vona *et al.*, 2000, reference does not disclose a reliable, sensitive and non-invasive prenatal diagnosis of foetal cells by: a) first analyzing the filtered cells to obtain a presumption of their foetal origin (by immunostaining or cytology), and b) pre-amplifying the genome of a single cell, which is individually collected from the filter, the foetal

origin of which would be presumed, and then c) using this single pre-amplified genome to carry out: i) the demonstration of the foetal origin of the single cell, the foetal origin of which is presumed, to confirm by marker amplification that the single cell is of foetal origin, and ii) if the foetal origin is thus demonstrated, to carry out an individual analysis of this pre-amplified genome for prenatal diagnosis.

Even more particularly, the Vona *et al.*, 2000, reference does not disclose, teach or suggest that the foetal origin could be established by: 1) determining a presumption of foetal origin (by immunostaining or cytology), and 2) if an individually collected cell is effectively presumed of being of foetal origin, demonstrating its foetal origin by amplification of appropriate markers (from a pre-amplified genome), and that 3) if the foetal origin of the single cell is demonstrated, carrying out the prenatal diagnosis by genetic analysis of the very same genome as the one for which a demonstration of foetal origin has been made.

Moreover, we respectfully submit that the Vona *et al.* reference does not disclose, teach or suggest that the foetal origin is established by a) the determination of a presumption of fetal origin (by immunostaining or cytology), and b) if the cell is effectively presumed of being of foetal origin, the demonstration of its fetal origin by amplification of appropriate makers (from a pre-amplified genome).

We submit that without foreknowledge of what matter constitutes the claimed invention, the person of average skill in the art could not arrive at the claimed invention from the combined teachings of the Kalionis reference and Vona *et al.*, 2000 references.

The instant invention is directed to a method for prenatal diagnosis, which is non-invasive, and which is markedly more reliable, sensitive, and specific than the prior art methods. This effectiveness is primarily due to the fact that the demonstration of foetal origin is made by marker amplification, and the demonstration of foetal origin and prenatal diagnosis are both performed on the very same genome, which has been pre-amplified from one single trophoblast

cell. The claimed invention advantageously does not require large volumes of blood (a volume of 1 to 10 mL is sufficient; see in the example on page 27 lines 16-17: 2 mL).

It is therefore respectfully submitted that the method of currently amended claim 1 is not obvious in light of the Kalionis and Vona *et al.*, 2000 references, and that the presently claimed invention provides previously unattainable advantages.

Because the combined references of Kalionis and Vona *et al.* do not disclose, teach or suggest each and every element of claim 1, claim 1 is not unpatentable over these references. Claims 4-5, 9-12 and 20-25 are dependent on claim 1 and are allowable at least by virtue of such dependency. Claims 2-3, 6, and 19 are cancelled. Accordingly, Applicants respectfully request that the rejection to claims 1-7, 9-12 and 19-25 be reconsidered and withdrawn.

Kalionis in view of Vona et al. 2000 and further in view of US Patent No. 5,614,628 to Bianchi

Claims 8, 13, 14, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona *et al.* 2000 and further in view of US Patent No. 5,614,628 to Bianchi ("Bianchi"). Applicants respectfully traverse.

The Kalionis and Vona *et al.* 2000 references were discussed above, and the arguments are incorporated herein by reference.

The Bianchi reference discloses a method of detecting the presence or absence of a foetal DNA sequence of interest from foetal DNA which is derived from a maternal peripheral blood sample. The reference also discloses that foetal cells can be isolated by antibody labeling, and flow cytometry sorting. The isolated foetal cells can be amplified to detect a selected target (e.g., abnormal gene portion) with a DNA probe.

The isolation method taught by the Bianchi reference is intended to provide an alternative to the use of morphology to isolate foetal cells. (Please see the first three paragraphs of the

"Background" section of the Bianchi reference). Therefore, the Bianchi reference teaches away from isolation by filtration according to morphology.

Therefore, we respectfully submit that a skilled artisan would not combine the Bianchi *et al.* reference with a reference such as the Vona *et al.*, 2000 reference.

It is further respectfully submitted that the Bianchi reference is directed to the isolation of undifferentiated hematopoietic cells, and more particularly, foetal nucleated cells, and that it does not relate to the isolation of an epithelial cell, such as a trophoblast or a syncytiotrophoblastic cell.

Hence, the method of amended claim 1 and those claims dependent thereon are not obvious in the light of the combination of Kalionis, Vona *et al.*, 2000 and Bianchi.

Kalionis in view of Vona et al. 2000 and Fodor

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona *et al.* 2000 and Fodor. Applicants respectfully traverse.

Claim 15 is dependent on claim 1, and therefore incorporates the features of claim 1. As discussed *supra*, the combined references of Kalionis and Vona *et al.* 2000 do not disclose the novel features of claim 1. Additionally, the Fodor reference does not singularly disclose the novel features of claim 1. Because the combined references do not disclose, teach or suggest each and every element of claim 1, claim 15 is at least allowable by virtue of its dependency on claim 1. Therefore, claim 15 is not obvious over Kalionis in view of Vona *et al.* 2000 and Fodor. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim 18 also is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona *et al.* 2000 and Pinkel. Applicants respectfully traverse.

As discussed above the Kalionis reference when combined with the Vona *et al.* 2000 reference do not disclose all of the elements of claim 1 to which claim 18 depends.

Pinkel discloses methods of comparative genome hybridization and the application of this method for prenatal diagnosis of fetal cells. However, Pinkel fails to disclose the method of claim 1 including steps of a) analyzing filtered cells to obtain a presumption of their foetal origin (by immunostaining or cytology), and b) pre-amplifying the genome of a single cell, which is individually collected from the filter, the foetal origin of which would be presumed, and then c) using this single pre-amplified genome to carry out: i) the demonstration of the foetal origin of the single cell, the foetal origin of which is presumed, to confirm by marker amplification that the single cell is of foetal origin, and ii) if the foetal origin is thus demonstrated, to carry out an individual analysis of this pre-amplified genome for prenatal diagnosis.

Claim 18 is dependent on claim 1 and incorporates the features of claim 1. Because the combination of Kalionis, Bona *et al.*, 2000 and Pinkel fail to disclose, teach or suggest each and every element of claim 1, claim 18 is not obvious over the combination of the above references. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Bisconte in view of FR 2,782,730 , (translated in US 2002/0028431) to Bisconte

Claims 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bisconte in view of FR 2,782,730 , (translated in US 2002/0028431) to Bisconte ("FR '730). Applicants respectfully traverse.

The Bisconte reference and FR '730 each disclose the filtering of blood to isolate pathogenic cells therefrom. However, neither of these references discloses the filtering of maternal blood to isolate foetal cells therefrom.

In contrast, independent claim 26 now relates to a process for obtaining foetal cells from maternal blood, which comprises filtering maternal blood to isolate foetal cells therefrom. The combination of Bisconte and FR '730 do not disclose this element.

Because the combined references do not disclose, teach or suggest each and every element claim 26 this claim is non-obvious over Bisconte and FR '730. Claims 27-29 are allowable, at least, by virtue of their dependency on claim 26. Applicants respectfully request this rejection be reconsidered and withdrawn.

SUMMARY

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution will be assisted thereby.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

If the Examiner has any questions concerning this application, the Examiner is requested to contact Gerald M. Murphy, Reg. No. 28,977 at the telephone number of (703) 205-8000.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

By _____
Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

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Statement under 37 C.F.R.. §§1.821-1.825